Varicella Outbreak Involving Two Dose Vaccine Recipients — Arkansas, 2006

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New ACIP Recommendations for Varicella Immunization

- June 2005
  - 2nd dose for children to control outbreaks, resources permitting
- June 2006
  - Routine 2-dose vaccination for all children
    - 1st dose: 12 – 15 months
    - 2nd dose: 4 – 6 years
    - Catch-up: >6 years

Arkansas Outbreak: September 2006

- 31 cases (as of 10/2)
  - 8 were 2-dose vaccine recipients
  - All reported mild or atypical disease
  - Elementary school complex (School A (pre-K), School B (K-3), School C (4-6)
    - Prior outbreak in same complex January 2006
    - Vaccination Clinic (per ACIP): ~ 400 students
      - Many received 2nd dose
- CDC invited to assist with current outbreak investigation
  - Objectives:
    - Confirm varicella in 2-dose vaccine recipient
    - Characterize vaccine effectiveness among 1- and 2-dose recipients

Outbreak Case Definition

- CSTE Case definition (acute maculopapulovesicular rash without other apparent cause) occurring between Sept 1 and Dec 18
  - In vaccinated persons disease may be:
    - Mild
    - Fewer than 50 skin lesions
    - Shorter duration of illness
    - Atypical in appearance (maculopapular with few or no vesicles)
- Operationally used 3 lesions as lower cut-off
- Lab confirmation
  - PCR (lesions, environmental samples)
  - IgM (blood, saliva)

Survey and Case Investigation

- Cases in students identified from:
  - Health Unit
  - School nurse
  - School wide survey:
    - Vaccination status & varicella history
    - Medical conditions
    - “Rashes, insect bites, bumps, spots, or blisters since start of school year”

- Case investigation
  - Clinical information
  - Medical conditions
  - Medications

Vaccination Records

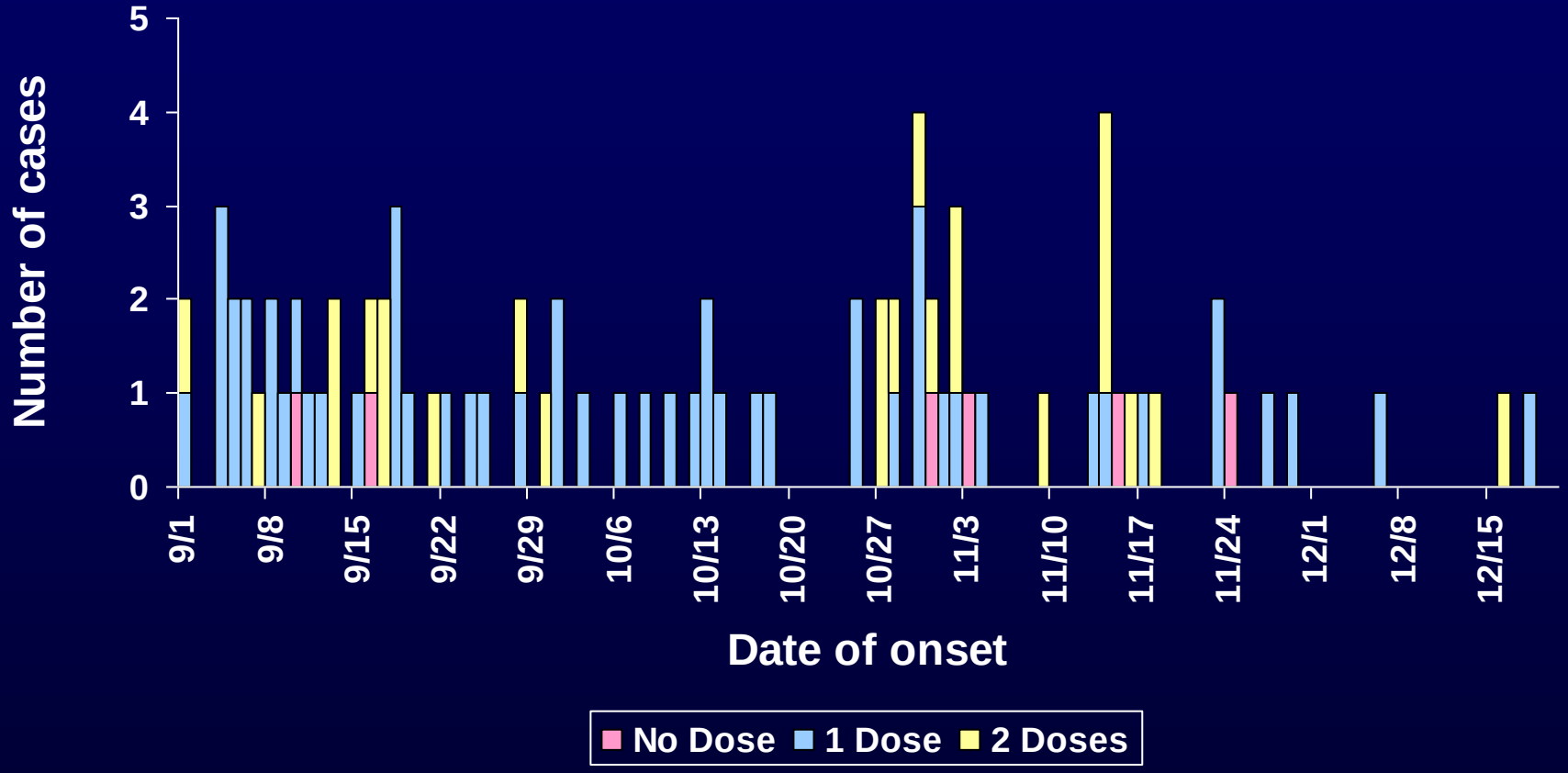
- Arkansas Immunization Registry
  - Vaccination status
  - Limited disease history (on unvaccinated cases)
- Alternate sources
  - Local paper records
  - Parental survey
- Vaccinations ≤ 42 days prior to rash onset
  - 1st dose = Unvaccinated
  - 2nd dose = Indeterminate

School-wide survey

- Overall response rate: 79%
  - School A (pre-K): 81%
  - School B (K-3): 84%
  - School C (4-6): 72%†
- Responders vs non responders
  - No difference in:
    - Gender
    - Vaccination status
  - Difference in:
    - Race/ethnicity – African-American children less likely to be responders (65% vs. 86% for white/Hispanic, $p < 0.001$)

† p<0.001

Reported varicella cases by rash onset date and vaccination status -- School Complex, Arkansas, 9/1-12/18/2006 (n=83*)



*2 cases with unknown rash onset dates excluded

Disease Severity

	No Prior Disease			
	1 dose (n=47)	2 dose (n=23)	Prior disease (n=15)	P-value
Number of lesions*				
<50	81% (38)	91% (21)	67% (10)	0.20
50-249	13% (6)	0% (0)	7% (1)	
250-499	0% (0)	0% (0)	0% (0)	
≥500	0% (0)	0% (0)	0% (0)	

*Number of lesions was unknown for 3 cases with 1-dose, 2 cases with 2-doses, and 4 cases with previous disease.

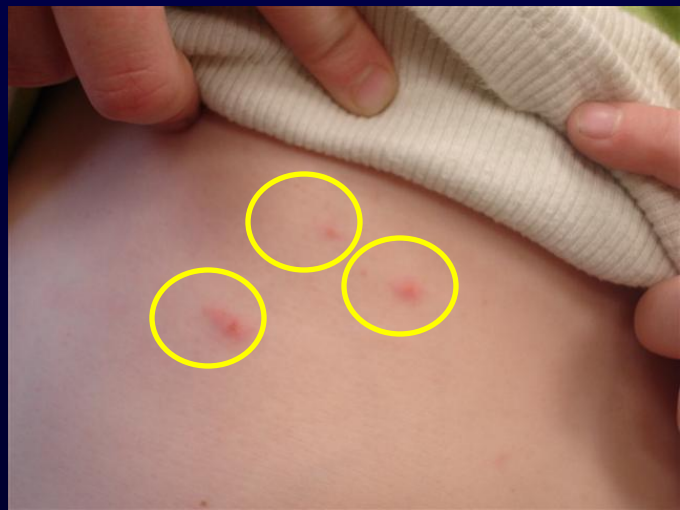
Disease Characteristics

	No Prior Disease			
	1 dose (n=47)	2 dose (n=23)	Prior disease (n=15)	P-value
Rash description				
Maculopapular	83% (39)	83% (19)	60% (9)	0.10
Vesicular	45% (21)	43% (10)	33% (5)	0.49
Itchy	87% (41)	87% (20)	100% (15)	0.23
Median rash duration, days (range)*	6 (1-13)	4 (1-16)	4 (1-7)	0.37
Fever	30% (14)	17% (4)	20% (3)	0.31

*Based on available data for 77 cases

Case Example Highlighting Challenges to Case Ascertainment

- Clinical characteristics of a 2 dose vaccine recipient
  - Only 4 papules at any one time
  - 1 to 2 vesicles
  - Itchy
  - Lasted 3 – 4 days
  - Specimens obtained on day of rash onset
    - Lesion: PCR positive
    - Saliva: Negative



Vaccination and Disease History of Cases (N=85)

Vaccination Status	Cases (%)	Attack rate
2 doses *- w/prior disease* *- w/unknown disease hx*	25 (29) *2* *1*	10.4
1 dose *- w/prior disease*	54 (64) *7*	14.6
0 doses *- w/prior disease*	6 (7) *6*	--

Vaccination Coverage

VACCINATION STATUS	SCHOOL			TOTAL N = 758*
	PRE-K N = 98	K – 3 N = 395	4 – 6 N = 265	
Unvaccinated	1%	2%	4%	3%
1 Dose	84%	54%	48%	56%
2 Doses**	15%	44%	48%	41%
Total Vaccinated	98%	97%	96%	97%

*Excluded:
106 students with history of disease
9 students with no vaccination data

** Includes 22 cases with 2nd dose within 42 days

Laboratory Results

- 27 cases tested: 6 positive
  - 5 PCR (lesion)
    - 1 two dose recipient
    - 3 one dose recipients
    - 1 unvaccinated with history of disease
  - 1 IgM serum spot (one dose recipient)

- Environmental samples from school and case-patient bedding
  - Pajamas and pillowcase PCR positive for wild-type virus

Vaccine Effectiveness Against Clinical Varicella Using Historic Attack Rates

- If we compare attack rates with historic rates for any varicella disease in unvaccinated:
  - AR_{unvacc} of 80%
    - 2 doses to unvaccinated:

      $VE_2 = 1 – (10.4\% / 80\%)$

      = **87% (95% CI: 80.5 to 91.4%)**
    - 1 dose to unvaccinated:

      $VE_1 = 1 – (14.6\% / 80\%)$

      = **81.8% (95% CI: 75.8 to 86.2%)**

Limitations

- May not have had sufficient power to detect differences
- Misclassification of case status
  - Broad clinical definition → False positives
  - Mild disease → False negatives
  - Lesion-based laboratory diagnostics only helpful while transient rash still present
- Misclassification of disease history
  - Based on parental report
- Response rate
  - Lower among School C students

Summary

- Varicella confirmed as cause of outbreak on both epidemiologic and laboratory criteria
  - Lab confirmation included two-dose recipient
- 85 cases identified
  - 25 (29%) two-dose recipients
  - Similar clinical picture in 1 vs. 2 dose recipients
- 97% school vaccination coverage
  - 41% two doses*
- 2-dose VE point estimate 5% points higher than 1-dose VE but overlapping confidence intervals

*Includes persons with 2nd dose < 42 days

Conclusions

- One of the largest varicella outbreaks investigated in recent years
- First U.S. outbreak reported with significant number of second dose vaccine recipients
- Case ascertainment challenging and may preclude evaluation of 2 vs. 1 risk reduction assessments in outbreak settings
- Moderate 2-dose coverage was insufficient to prevent this outbreak

Next steps

- Additional vaccine effectiveness studies needed
  - Range of VE for 1-dose: 44-100% from >30 studies

- Need to monitor the number and size of outbreaks as a key outcome to assess effects of the routine 2 dose policy

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